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10/085,239	02/27/2002	Simon Ward	674569-2001	1714

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EXAMINER	
ASHEN, JON BENJAMIN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/085,239	WARD ET AL.	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-39 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-39 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-8(a), 10, 16, 22-28, 30-33 and 39 are drawn to a method of treatment comprising reducing the endogenous level or activity of retinoic acid in a cell of a patient using an immunoglobulin, classifiable in class 424, subclass 130.1.

II. Claims 1-8(b-d), 10, 16, 22-28, 30-33 and 39 are drawn to a method of treatment comprising reducing the endogenous level or activity of retinoic acid in a cell of a patient using a peptide comprising a sequence from a retinol protein binding region of a retinol binding protein, classifiable in class 514, subclass 14.

III. Claims 1-8(e-f), 10, 16, 22-28, 30-33 and 39 are drawn to a method of treatment comprising reducing the endogenous level or activity of retinoic acid in a cell of a patient using an antisense molecule, classified in class 514, subclass 44.

IV. Claims 1-8(g), 10, 16, 22-28, 30-33 and 39 are drawn to a method of treatment comprising reducing the endogenous level or activity of retinoic acid in a cell of a patient using inhibitory molecules of the retinoic acid biosynthetic pathway, classifiable in class 568, subclass 448.

V. Claims 11-15, 17, 19 and 35-38 are drawn to an immunoglobulin agent or antagonist of a retinol binding protein receptor capable of reducing the endogenous level or activity of retinoic acid in a cell of a patient, classifiable in class 424, subclass 130.1.

VI. Claims 11-15, 17, 19 and 35-38 are drawn to a peptide agent or antagonist of a retinol binding protein receptor capable of reducing the endogenous level or activity of retinoic acid in a cell of a patient, classifiable in class 530, subclass 14.

VII. Claims 11-15, 17, 19 and 35-38 are drawn to an antisense molecule agent or antagonist of a retinol binding protein receptor capable of reducing the endogenous level or activity of retinoic acid in a cell of a patient, classified in class 536, subclass 24.5.

VIII. Claims 11-15, 17, 19 and 35-38 are drawn to a known inhibitory molecule agent or antagonist of a retinol binding protein receptor capable of

reducing the endogenous level or activity of retinoic acid in a cell of a patient, classifiable in class 568, subclass 448.

IX. Claim 18 is drawn to a method of identifying a compound capable of lowering the endogenous level of retinoic acid in a cell comprising contacting a cell expressing a retinol binding protein receptor with a candidate compound and determining the level of retinoic acid in said cell, classifiable in class 435, subclass 7.1.

X. Claim 18 is drawn to a method of identifying a compound capable of lowering the endogenous level of retinoic acid in a cell comprising determining the level of competitive binding of a candidate compound to a retinol binding protein receptor in the presence of retinol binding protein, classifiable in class 435, subclass 7.1.

XI. Claim 18 is drawn to a method of identifying a compound capable of lowering the endogenous level of retinoic acid in a cell comprising exposing a cell expressing retinol dehydrogenase to a compound and determining if retinal levels in a cell are reduced, classifiable in class 435, subclass 7.4.

1. Claims 21 link(s) the inventions of groups I-IV that are methods of treatment comprising lowering the endogenous level or activity of retinoic acid in a cell. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claim 21. Claim 29 link(s) inventions of groups I-IV that are the diseases, disorders or conditions treated by lowering endogenous levels of retinoic acid in a cell and that are listed in claims 30, 32 and 39. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claim 29. Claim 20 link(s) inventions of groups V-VIII that compounds capable of lowering the endogenous level or activity of retinoic acid in a cell. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claim 20. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

2. Claims 1-8, 10, 16, 22-28, 30-33 and 39 are generic to groups I-IV. Claims 11-15, 17, 19 and 35-38 are generic to groups V-VIII. Claim 18 is generic to groups IX-XI. These claims will be examined as they read on the subject matter of the group elected.

The inventions are distinct, each from the other because of the following reasons:

3. Inventions of groups I-IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). The inventions of groups I-IV are drawn to methods of treatment comprising reducing the endogenous level or activity of retinoic acid in a cell of a patient using an immunoglobulin (group I, claim 8a), a peptide comprising a sequence from a retinol protein binding region of a retinol binding protein (group II, claim 8b-d), an antisense molecule (group III, claim 8e-f) or a known inhibitory molecule of a retinoic acid biosynthetic enzyme that are the molecules listed in claim 8(g). In the instant case the different inventions are not disclosed as capable of use together and have different functions. A method for reducing the endogenous level or activity of retinoic acid in a cell of a patient using an immunoglobulin antagonist functions by immunoglobulin binding to an antigenic site of a retinol binding protein receptor (group I), said method using a peptide antagonist comprising a sequence from a receptor binding region of retinol binding protein functions by competitive inhibition of retinol binding protein (group II), said method using an antisense molecule functions by modulation of gene expression of the retinol binding protein receptor (group III) and said method using

known inhibitory molecule antagonists of enzymes involved in retinoic acid biosynthesis functions by inhibiting retinoic acid biosynthesis. Therefore each invention is patentably distinct.

Furthermore, searching the inventions of groups I-IV would impose a serious search burden. In the instant case, prior art searches of methods utilizing antibodies, peptide fragments of retinol binding protein, antisense molecules and known inhibitory molecules listed in claim 8(g) are not coextensive. Search of each of these inventions would require different key word searches of distinct method steps in divergent patent and non-patent literature databases and subsequent in-depth analysis of unrelated literature, placing a serious burden on the Office in terms of both search and examination of the unrelated prior art. As such, it would be burdensome to perform examination of the inventions of groups I-IV together.

4. Inventions of groups V-VIII are unrelated. Inventions of groups V-VIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). The inventions of groups V-VIII are drawn to an immunoglobulin antagonist of a retinol binding protein receptor (group V), a peptide antagonist of a retinol binding protein receptor (group VI), an antisense molecule (group VII) or a known inhibitory molecule antagonist of a retinoic acid biosynthetic enzyme as listed in claim 15(g) (group VIII). In the instant case the different inventions are not disclosed as capable of use together and have different

functions. An immunoglobulin antagonist functions as an antibody (group V), a peptide antagonist functions as a competitive inhibitor of retinol binding protein to its receptor (group VI), an antisense molecule functions to modulate gene expression of a retinol protein binding receptor (group VII) and a known inhibitory molecule as listed in claim 15(g) functions by antagonizing an enzyme in the retinoic acid biosynthetic pathway (group VIII). Therefore, the inventions are patentably distinct.

Furthermore, searching the inventions of groups V-VIII would impose a serious search burden. In the instant case, prior art searches of antibodies, peptide fragments of retinol binding protein, antisense molecules and known inhibitory molecules listed in claim 15(g) are not coextensive. Search of each of these inventions would require different key word searches in divergent patent and non-patent literature databases and subsequent in-depth analysis of unrelated literature, placing a serious burden on the Office in terms of both search and examination of the unrelated prior art. As such, it would be burdensome to perform examination of the inventions of groups V-VIII together.

5. Inventions of groups IX-XI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). The inventions of group IX-XI are drawn to methods of identifying a compound capable of lowering the endogenous level of retinoic acid in a cell comprising contacting a cell with a candidate compound and determining the level of retinoic acid in said cell

(group IX), determining the level of competitive binding of a candidate compound to a retinol binding protein receptor in the presence of retinol binding protein (group X) or exposing a cell expressing retinol dehydrogenase to a compound and determining if retinal levels in a cell are reduced (group XI). In the instant case the different inventions are not disclosed as capable of use together and will have different modes of operation comprising distinct steps and utilizing different products. The invention of group IX operates by determining the level of retinoic acid in a cell, the invention of group X operates by determining the level of binding of a candidate compound to a retinol binding protein receptor in the presence of retinol binding protein and the invention of group XI operates by determining the levels of retinal in a cell.

Furthermore, searching the inventions of groups IX-XI would impose a serious search burden. In the instant case, prior art searches of the different methods of each of the inventions of groups IX-XI are not coextensive. Search of each of these inventions would require different key word searches of distinct steps from divergent patent and non-patent literature databases and subsequent in-depth analysis of unrelated literature, placing a serious burden on the Office in terms of both search and examination of the unrelated prior art. As such, it would be burdensome to perform examination of the inventions of groups IX-XI together.

6. Inventions of groups I-IV and V-VIII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another

materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). The inventions of groups I-IV and V-VIII are outlined above. In the instant case each of the products of groups V-VIII can be used in a materially different process of using that product. The immunoglobulin of group V can be used to determine tissue and cell specific protein expression, petptide or peptide fragments of group VI can be used to identify compounds that would bind to retinol binding protein receptors, the antisense molecule of group VII can be used for a tissue or cell specific hybridization assay of gene expression and the inhibitory molecules of group VIII can be used *in vitro* to study enzyme kinetics.

Furthermore, searching any of the inventions of groups I-VI together with any of the inventions of groups V-VIII would impose a serious search burden. In the instant case, prior art searches of methods of treatment using antibodies, peptide fragments of retinol binding protein, antisense molecules or the known inhibitory molecules listed in claim 11(g) are not coextensive with prior art searches of each of these products. Search of each of these inventions would require different key word searches of each compound and of each distinctive step of each method using divergent patent and non-patent literature databases. The different searches would then require subsequent in-depth analysis of the unrelated prior art literature, placing a serious burden on the Office in terms of both search and examination. As such, it would be burdensome to perform examination of any of the inventions of groups I-VI together with any of the inventions of groups V-VIII.

7. Inventions of groups I-IV and IX-XI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). The inventions of groups I-IV are methods of treatment as outlined above. The inventions of groups XI-IX are drawn to methods of identifying a compound capable of lowering the endogenous level of retinoic acid in a cell as outlined above. In the instant case the methods of groups I-IV and IX-XI are not disclosed as capable of use together and have different functions. The inventions of groups I-IV are methods that function to provide a treatment. The inventions of groups IX-XI are methods that function to identify compounds.

Furthermore, searching any of the methods of groups I-IV together with any of the methods of groups IX-XI would impose a serious search burden. In the instant case, prior art searches of the different methods of each of the inventions of groups I-IV and groups XII-XIV are not coextensive. Search of each of these inventions would require different key word searches of distinct method steps from divergent patent and non-patent literature databases followed by subsequent in-depth analysis of said distinct steps from unrelated prior art literature. This would place a serious burden on the Office in terms of both search and examination of the prior art literature. As such, it would be burdensome to perform a search and examination any of the methods of groups I-IV together with any of the methods of groups IX-XI.

8. Inventions of groups V-VIII and IX-XI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). The inventions of groups V-VIII and groups IX-XI are described above. In the instant case, the compounds that are the inventions of groups V-VIII and the methods of groups IX-XI are not disclosed as capable of use together and have different functions. The compounds that are the inventions of groups V-VIII all function to lower the endogenous levels or activity of retinoic acid in a cell. The methods that are the inventions of groups IX-XI all function as methods for identifying a compound capable of lowering the endogenous levels or activity of retinoic acid in a cell.

Furthermore, searching any of the compounds of groups V-VIII together with any of the methods of groups IX-XI would impose a serious search burden. In the instant case, prior art searches of the different compounds of each of the inventions of groups V-VIII and each of the methods of groups IX-XI are not coextensive. Search of each of these inventions would require different key word searches of compounds and of distinct method steps from divergent patent and non-patent literature databases. The results of these different searches would then require subsequent in-depth analysis of unrelated prior art literature, placing a serious burden on the Office in terms of both search and examination. As such, it would be burdensome to perform a search and examination any of the inventions of groups V-VIII together with any of the inventions of groups IX-XI.

Therefore, because these inventions are distinct for the reasons given above, have acquired a separate status in the art as shown by their different classifications and would require, as outlined above, divergent searches of prior art sequence, patent and non-patent literature databases which would place a serious and undue administrative burden examiner, restriction for examination purposes as indicated is proper.

9. Groups I-VIII are further restricted as follows. Claims 6, 7, 8, 11, 32 and 39 all contain multiple, patently distinct inventions that are enzymes of the retinoic acid biosynthetic pathway (claims 6,7), methods of lowering the endogenous level or activity of retinoic acid in a cell (claim 8), compounds capable of lowering the endogenous level or activity of retinoic acid in a cell (claim 11) and diseases, disorders or conditions that are to be treated by methods that are the instant inventions of groups I-IV as claimed (claim 39). Although the multiple, patently distinct inventions listed in claims 7, 8, 11 and 39 are listed in Markush group format, claims 7, 8, 11 and 39 are subject to additional restriction since they are not considered to be proper genus/Markush claims. See MPEP §803.02 – Practice re Markush type claims.

Since the decisions *In re* Weber, 580 F. 2d 455, 198 USPQ 328 (CCPA 1978) and *In re* Haas, 580 F. 2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. In re Harnisch, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. Application. & Int. 1984). Broadly, unity of invention exists where compounds included within a

Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

In regards to the instant application, the retinol dehydrogenases, alcohol dehydrogenases and retinal dehydrogenases listed in claim 7, the antagonists listed in claim 8 (a-g) and the antagonists listed in claim 15(a-g) do not share amongst themselves, a common utility or a substantial structural feature that is disclosed as being essential to that utility. In regards to retinol and retinal dehydrogenases, the specification discloses that "the substrate preference and expression domains of these enzymes vary," indicating that the structural feature of these enzymes that is related to the common utility (substrate binding to catalyze a dehydrogenase reaction), is variable and therefore, not shared. Absent evidence to the contrary, the same substrate specificity would be expected from alcohol dehydrogenase enzymes.

Claim 8 is drawn to methods of treatment wherein the antagonist of the retinol binding protein receptor is an immunoglobulin (8a), a peptide (8b-d), an antisense molecule (8e-f) or a known inhibitory molecule of one of the enzymes in the retinoic acid biosynthetic pathway (8g). Although the common utility of being an antagonist of a retinol binding protein receptor is asserted for each member of the Markush group listed, the specification discloses the function of the molecules in 8(g) as known inhibitors of enzymes in the retinoic acid biosynthetic pathway (pgs. 22-24). There appears to be no disclosure of an antisense molecule that is an antagonist of a retinol binding protein receptor. Therefore, the compounds claimed in claim 8 (a-g) do not

share the asserted common utility of being antagonists of retinol binding protein receptors.

In regards to claim 15 (a-g), there is no disclosure of any shared substantial structural features among immunoglobulins, peptides, antisense molecules or inhibitory molecules of the retinoic acid biosynthetic pathway that would be essential to the asserted common utility of being an antagonist.

In regards to claim 39, the multiple diseases, disorders and conditions as claimed encompass a broad genus of diseases for which the representative species listed are not sufficiently few in number or so closely related that a search and examination of the entire claim could be made without serious burden. Consequently, restriction within claims 6-8, 15 and 39 is proper because, in lacking unity of invention, these claims are drawn to multiple, patentably distinct inventions.

Additionally, the multiple response elements listed in claim 32 constitute a genus of patentably distinct response elements for which the representative species listed are not sufficiently few in number or so closely related that a search and examination of the entire claim could be made without serious burden. Each of the response elements listed would require a separate key word and sequence search from divergent patent and non-patent literature databases requiring subsequent in-depth analysis of unrelated prior art, placing a serious burden on the Office in terms of both search and examination. As such, it would be burdensome to perform a search and examination of the multiple response elements listed in claim 32.

Therefore, if electing any of groups I-IV, Applicant is required to elect, in accordance with restriction to a single invention as set forth above: 1) a single enzyme of the retinoic acid biosynthetic pathway listed in claims 6 and 7 that is to be antagonized by the method as claimed, 2) a single nuclear receptor response element listed in claim 32, the abnormal or overexpression of which corresponds with 3) a single disease, disorder or condition from claim 39, that is treated by the claimed method. If electing either of groups IV or VIII, applicant is further restricted to a single inhibitory molecule of an enzyme in the retinoic acid biosynthetic pathway (listed in claims 8(g) and 15(g) respectively), that must correspond in scope with the elected invention; i.e., that is an inhibitory molecule of the enzyme of the retinoic acid biosynthetic pathway elected from claims 6 and 7 that is to be antagonized to provide a method of treatment related to a disease, disorder or condition that corresponds with the abnormal or overexpression of a nuclear receptor response element.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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